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Guidelines

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Summary document prepared by the Czech Society of Cardiology☆

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Contents

1 Preamble

Guidelines help physicians to make decisions in their practice, but do not override the responsibility of health professionals to make decisions and to follow the rules and regulations applicable to drugs and devices. The level of evidence and the strength of recommendation are outlined in Tables 1 and 2.

The Czech Society of Cardiology endorses ESC guidelines and prepares condensed summaries. For details and for references see the original ESC document [1].

2 Introduction

Clinically relevant new aspects of 2014 version relate to:

(1) Predisposing factors for venous thromboembolism
(2) Simplification of clinical prediction rules
(3) Age-adjusted D-dimer cut-offs
(4) Sub-segmental pulmonary embolism (PE)
(5) Incidental, clinically unsuspected PE
(6) Advanced risk stratification of intermediate-risk PE
(7) Initiation of treatment with vitamin K antagonists
(8) The use of new oral anticoagulants
(9) Efficacy and safety of reperfusion treatment for patients at intermediate risk
(10) Early discharge and outpatient treatment of PE
(11) Current management of chronic thromboembolic pulmonary hypertension
(12) Management of PE in pregnancy and in cancer patients

2.1 *Epidemiology*

Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most frequent cardiovascular disease with an overall annual incidence of 100–200 per 100,000 inhabitants. PE is a major cause of mortality, morbidity, and hospitalization in Europe.

2.2 *Predisposing factors*

A list of predisposing (risk) factors for VTE is shown in Web Table 1. The presence of persistent—as opposed to major, temporary—risk factors may affect the decision on the duration of anticoagulation therapy after a first episode of PE.

2.3 *Natural history*

Following the acute PE episode, resolution of pulmonary thrombi, as evidenced by lung perfusion defects, is frequently incomplete. The incidence of confirmed chronic thromboembolic pulmonary hypertension (CTEPH) after unprovoked PE is currently estimated at approximately 1.5%, with most cases appearing within 24 months of the index event. The cumulative proportion of patients with early recurrence of VTE (on anticoagulant treatment) amounts to 2.0% at 2 weeks, 6.4% at 3 months and 8% at 6 months.

2.4 *Pathophysiology*

Acute PE interferes with both the circulation and gas exchange. Right ventricular (RV) failure due to pressure overload is considered the primary cause of death in severe PE. The abrupt

Table 1 – Classes of recommendations.

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or diverging opinion about the usefulness/efficacy of the given treatment of procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 – Levels of evidence.

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Web Table 1 – Predisposing factors for VTE.

Strong risk factors (odds ratio >10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous venous thromboembolism
Spinal cord injury

Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Auto–immune diseases
Blood transfusion
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Infection (specifically pneumonia, urinary tract infection or HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Oral contraceptive therapy
Paralytic stroke
Postpartum period
Superficial vein thrombosis
Thrombophilia

Weak risk factors (odds ratio <2)
Bed rest >3 days
Diabetes mellitus
Hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

increase in pulmonary vascular resistance results in RV dilation, which alters the contractile properties of the RV myocardium. The detrimental effects of acute PE on the RV myocardium and the circulation are summarized in Fig. 1.

2.5 *Clinical classification of pulmonary embolism severity*

The clinical classification of the severity of an episode of acute PE is based on the estimated PE-related early mortality risk defined by in-hospital or 30-day mortality (Fig. 2).

3 Diagnosis

3.1 *Clinical presentation*

PE may escape prompt diagnosis since the clinical signs and symptoms are non-specific (Table 3). In most patients, PE is suspected on the basis of dyspnoea, chest pain (requiring differential diagnosis with acute coronary syndrome (ACS) or aortic dissection), pre-syncope or syncope, and/or haemoptysis. Arterial hypotension and shock are rare but important clinical presentations, since they indicate central PE and/or a severely reduced haemodynamic reserve. Syncope is infrequent, but may occur regardless of the presence of haemodynamic instability.

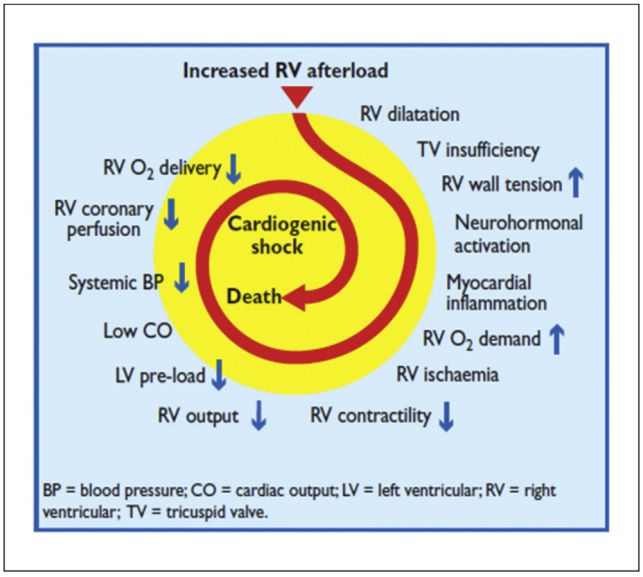

Fig. 1 – Key factors contributing to haemodynamic collapse in acute pulmonary embolism.

3.2 *Assessment of clinical probability*

Despite the limited sensitivity and specificity of individual symptoms, signs, and common tests, the combination of

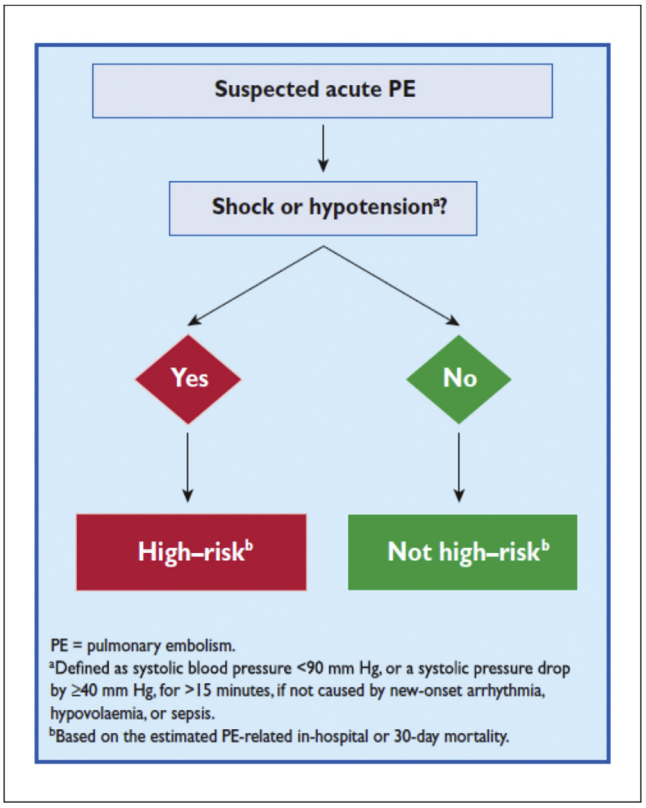

Fig. 2 – Initial risk stratification of acute PE.

Table 3 – Clinical characteristics of patients with suspected PE in the emergency department.

Feature	PE confirmed (n = 1880)	PE not confirmed (n = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

Adapted from Pollack et al. (2011).
DVT = deep vein thrombosis.

findings evaluated by clinical judgement or by the use of prediction rules allows to classify patients with suspected PE into distinct categories of clinical or pre-test probability that correspond to an increasing actual prevalence of confirmed PE. The most frequently used prediction rule is the one offered by Wells et al. (Table 4). This rule has been validated extensively using both a three-category scheme (low, moderate, or high clinical probability of PE) and a two category scheme (PE likely or unlikely). The revised Geneva rule is also simple and standardized (Table 4).

3.3 *D-dimer testing*

The negative predictive value of D-dimer testing is high and a normal D-dimer level renders acute PE or DVT unlikely (see also Section 3.10.2). The positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE. The quantitative enzyme-linked immunosorbent assay (ELISA) have a diagnostic sensitivity of 95% or better and can therefore be used to exclude PE in patients with either a low or a moderate pre-test probability (Table 5). Recent evidence suggests using age-adjusted cut-off values (age × 10 μg/l above 50 years) to improve the performance of D-dimer testing in the elderly.

3.4 *Computed tomographic pulmonary angiography*

Computed tomographic angiography (MDCTA) has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to at least the segmental level. In patients with a low or intermediate clinical probability of PE as assessed by the Wells rule, a negative MDCTA had a high negative predictive value for PE (96% and 89%, respectively),

Table 4 – Clinical prediction rules for PE.

Items	Clinical decision rule points	
	Original version	Simplified version
Wells rule		
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2
Revised Geneva Score		
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–2	0–2
PE likely	≥6	≥3

b.p.m. = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

Table 5 – Diagnostic yield of various D-dimer assays in excluding acute PE according to outcome studies.

Study	D-dimer assay	Patients n	PE prevalence %	PE excluded by D-dimer and clinical probability[a] n (%)	Three-month thromboembolic risk % (95% CI)
Carrier, 2009 (meta-analysis)	Vidas Exclusion	5622	22	2246 (40)	0.1 (0.0–0.4)
Kearon, 2006; Wells, 2001	SimpliRed	2056	12	797 (39)	0.0 (0.0–0.5)
Leclercq, 2003; ten Wolde, 2004; van Belle, 2006	Tinaquant	3508	21	1123 (32)	0.4 (0.0–1.0)

CI = confidence interval; PE = pulmonary embolism.
[a] Low or intermediate clinical probability, or PE unlikely, depending on the studies.

whereas this was only 60% in those with a high pre-test probability. Conversely, the positive predictive value of a positive MDCTA was high (92–96%) in patients with an intermediate or high clinical probability but much lower (58%) in patients with a low pre-test likelihood of PE. Therefore, clinicians should be particularly cautious in case of discordance between clinical judgement and the MDCTA result. A negative MDCTA is an adequate criterion for excluding PE in patients with a non-high clinical probability of PE. MDCTA showing PE at the segmental or more proximal level is adequate proof of PE in patients with a non-low clinical probability; however, the positive predictive value of MDCTA is lower in patients with a low clinical probability of PE, and further testing may be considered, especially if the clots are limited to segmental or sub-segmental arteries.

3.5 *Lung scintigraphy*

Ventilation–perfusion scintigraphy (V/Q scan) is an established diagnostic test for suspected PE. It is safe and few allergic reactions have been described. The V/Q scan may preferentially be applied in outpatients with low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnancy, in patients with history of contrast medium-induced anaphylaxis and strong allergic history, in severe renal failure, and in patients with myeloma and paraproteinaemia. Lung scan results are frequently classified according to the criteria established in the PIOPED study: normal or near-normal, low, intermediate (non-diagnostic), and high probability of PE but a proposed classification is preferable: normal scan (excluding PE), high probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan. Prospective clinical outcome studies suggested that it is safe to withhold anticoagulant therapy in patients with a normal perfusion scan. Performing only a perfusion scan is acceptable in patients with a normal chest X-ray.

3.6 *Pulmonary angiography*

Pulmonary angiography is more often used to guide percutaneous catheter-directed treatment of acute PE.

3.7 *Magnetic resonance angiography*

This technique, although promising, is not yet ready for clinical practice.

3.8 *Echocardiography*

Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. Because of the reported negative predictive value of 40–50%, a negative result cannot exclude PE. On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE. RV dilation is found in at least 25% of patients with PE, and its detection, either by echocardiography or MDCTA, is useful for risk stratification of the disease. Echocardiographic examination is not recommended as part of the diagnostic work-up in haemodynamically stable, normotensive patients with suspected (not high-risk) PE. This is in contrast to suspected high-risk PE, in which the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of haemodynamic instability. Mobile right heart thrombi essentially confirm the diagnosis of PE and their presence is associated with RV dysfunction and high early mortality.

3.9 *Compression venous ultrasonography*

In the majority of cases, PE originates from DVT in a lower limb. In a study using venography, DVT was found in 70% of patients with proven PE. CUS shows a DVT in 30–50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing.

3.10 *Diagnostic strategies*

Table 6 provides the necessary evidence for alternative evidence-based diagnostic algorithms.

3.10.1 *Suspected pulmonary embolism with shock or hypotension*

The proposed strategy is shown in Fig. 3. Suspected high-risk PE is an immediately life-threatening situation. The clinical probability is usually high, and the differential diagnosis includes acute valvular dysfunction, tamponade, acute coronary syndrome (ACS), and aortic dissection. The most useful initial test in this situation is bedside transthoracic echocardiography, which will yield evidence of acute pulmonary hypertension and RV dysfunction. In a highly unstable patient, echocardiographic evidence of RV dysfunction is sufficient to prompt immediate reperfusion without further testing. This decision may be strengthened by the (rare) visualization of right heart thrombi. Ancillary bedside imaging tests include transoesophageal echocardiography which, if available, may allow direct visualization of thrombi in the pulmonary artery and its main branches, and bedside CUS, which can detect proximal DVT. As soon as the patient can be stabilized by supportive treatment, final confirmation of the diagnosis by CT angiography should be sought.

3.10.2 *Suspected pulmonary embolism without shock or hypotension*

Computed tomographic angiography has become the main thoracic imaging test for investigating suspected PE (Fig. 4). In patients admitted to the emergency department, plasma D-dimer measurement, combined with clinical probability assessment, is the logical first step and allows PE to be ruled out in around 30% of patients. D-dimer should not be measured in patients with a high clinical probability. It is also less useful in hospitalized patients because the number needed to test to obtain a clinically relevant negative result is high. MDCTA is the second-line test in patients with an elevated D-dimer level and the first-line test in patients with a high clinical probability. CT angiography is considered to be diagnostic of PE when it shows a clot at least at the segmental level of the pulmonary arterial tree. Performing CUS before MDCTA may be an option in patients with relative contraindications for CT such as in renal failure, allergy to contrast

Table 6 – Validated diagnostic criteria (based on non-invasive tests) for diagnosing PE in patients without shock or hypotension according to clinical probability.

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
***D*-dimer**					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–
Chest CT angiography					
Normal multidetector CT alone	+	+	±	+	±
V/Q scan					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–	+	–
Confirmation of PE					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

+/green = valid diagnostic criterion (no further testing required); –/red = invalid criterion (further testing mandatory); ±/yellow = controversial criterion (further testing to be considered).
[a] Low or intermediate probability lung scan according to the PIOPED classification.
CT = computed tomographic; CUS = proximal lower limb venous ultrasonography; DVT = deep vein thrombosis; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; V/Q scan = ventilation–perfusion scintigram.

dye, or pregnancy. In centres in which V/Q scintigraphy is readily available, it remains a valid option for patients with an elevated D-dimer and a contraindication to MDCTA. V/Q scintigraphy may be preferred over MDCTA to avoid unnecessary radiation, particularly in younger and female patients in whom thoracic CT may raise the lifetime risk of breast cancer.

3.11 *Areas of uncertainty*

The diagnostic value and clinical significance of sub-segmental defects on MDCTA are still under debate. The value and cost-effectiveness of CUS in suspected PE should be further clarified. Finally, 'triple rule-out' (for coronary artery disease, PE and aortic dissection) CT angiography for patients presenting with nontraumatic chest pain appears to be accurate for the detection of coronary artery disease.

4 Prognostic assessment

4.1 *Clinical parameters*

PE severity index (PESI; Table 7) is the most extensively validated score to date. A simplified version—sPESI has been developed and validated. Clinical symptoms and signs of acute RV failure (e.g. persistent arterial hypotension and cardiogenic shock) indicate a high risk of early death. Further, syncope and tachycardia, as well as clinical parameters related to pre-existing conditions and comorbidity, are associated with an unfavourable short-term prognosis.

4.2 *Imaging of the right ventricle by echocardiography or computed tomographic angiography*

Echocardiographic findings used to risk stratify patients with PE include RV dilation, an increased RV–LV diameter ratio, hypokinesia of the free RV wall, increased velocity of the jet of tricuspid regurgitation, decreased tricuspid annulus plane systolic excursion, or combinations of the above.

RV dysfunction detected by echocardiography is associated with increased short-term mortality in patients without haemodynamic instability, but its overall positive predictive value is low (Table 8). Right-to-left shunt through a patent foramen ovale and the presence of right heart thrombi are associated with increased mortality in patients with acute PE.

MDCTA may detect RV enlargement as an indicator of RV dysfunction and prognosis (Table 8).

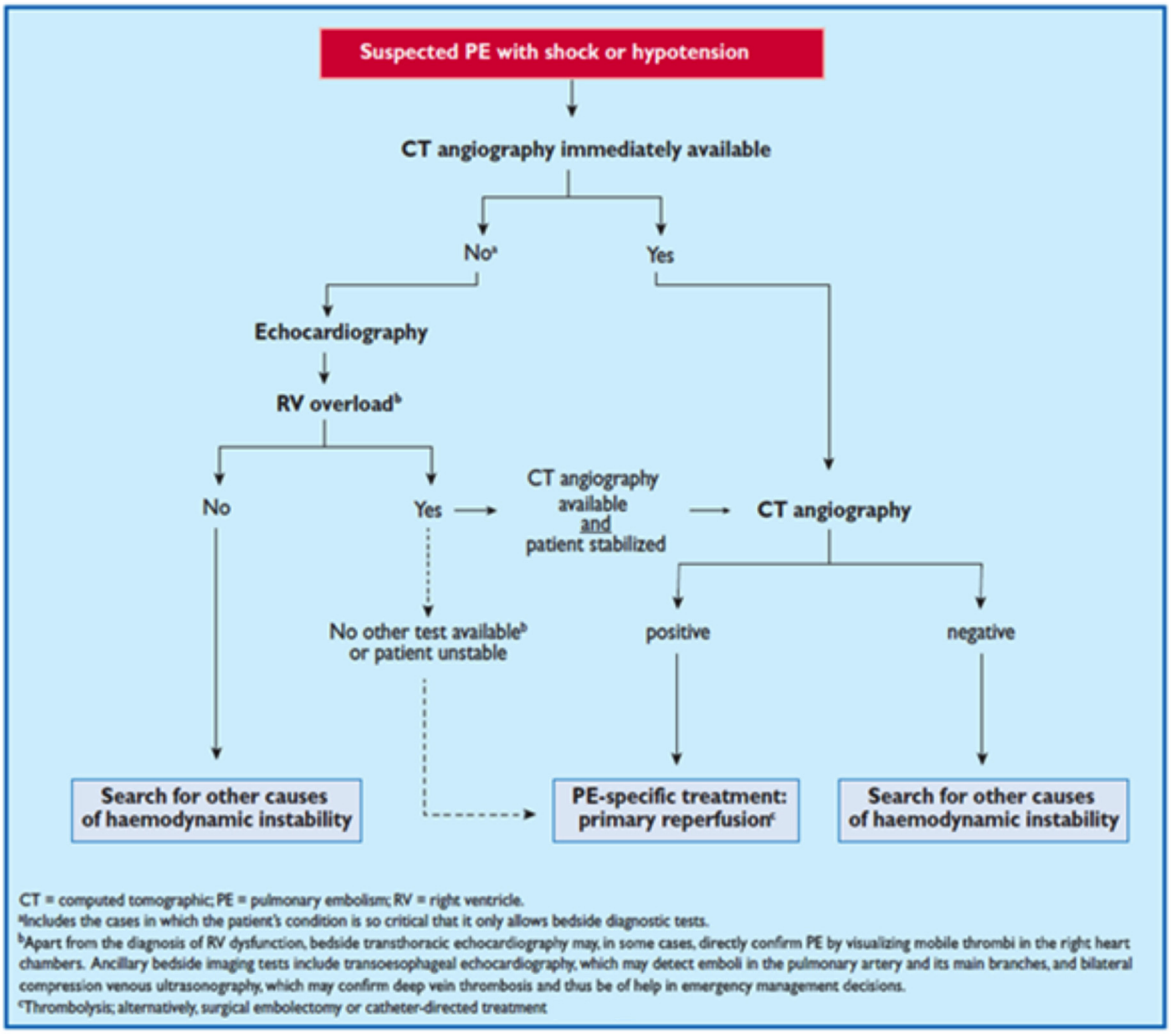

Fig. 3 – Proposed diagnostic algorithm for patients with suspected high-risk PE, i.e. presenting with shock or hypotension.

4.3 *Laboratory tests and biomarkers*

4.3.1 *Markers of right ventricular dysfunction*

A meta-analysis found that 51% of 1132 unselected patients with acute PE had elevated BNP or NT-proBNP concentrations on admission. These patients had a 10% risk of early death and a 23% risk of an adverse clinical outcome. In normotensive patients with PE, the positive predictive value of elevated BNP or NT-proBNP for early mortality is low (Table 8). Low levels of BNP or NT-proBNP can identify patients with a favourable short-term clinical outcome based on their high negative predictive value.

4.3.2 *Markers of myocardial injury*

A meta-analysis (1985 patients) showed elevated cardiac troponin concentrations in approximately 50% of PE patients (Table 8). Elevated troponin concentrations were associated with high mortality both in unselected patients and in haemodynamically stable patients; however, other reports have suggested a limited prognostic value of elevated troponins in normotensive patients. Negative predictive value of troponins is high. Heart-type fatty acid-binding protein (H-FABP) was also found to possess prognostic value in acute PE.

4.3.3 *Other (non-cardiac) laboratory biomarkers*

Elevated serum creatinine levels and a decreased glomerular filtration rate are related to 30-day all-cause mortality in acute PE. Elevated neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C are also of prognostic value. Elevated D-dimer concentrations were associated with increased short-term mortality, while levels <1500 ng/mL had a negative predictive value of 99% for excluding three-month all-cause mortality.

4.4 *Combined modalities and scores*

Various combinations of clinical findings with imaging and laboratory tests have been proposed and tested in an attempt

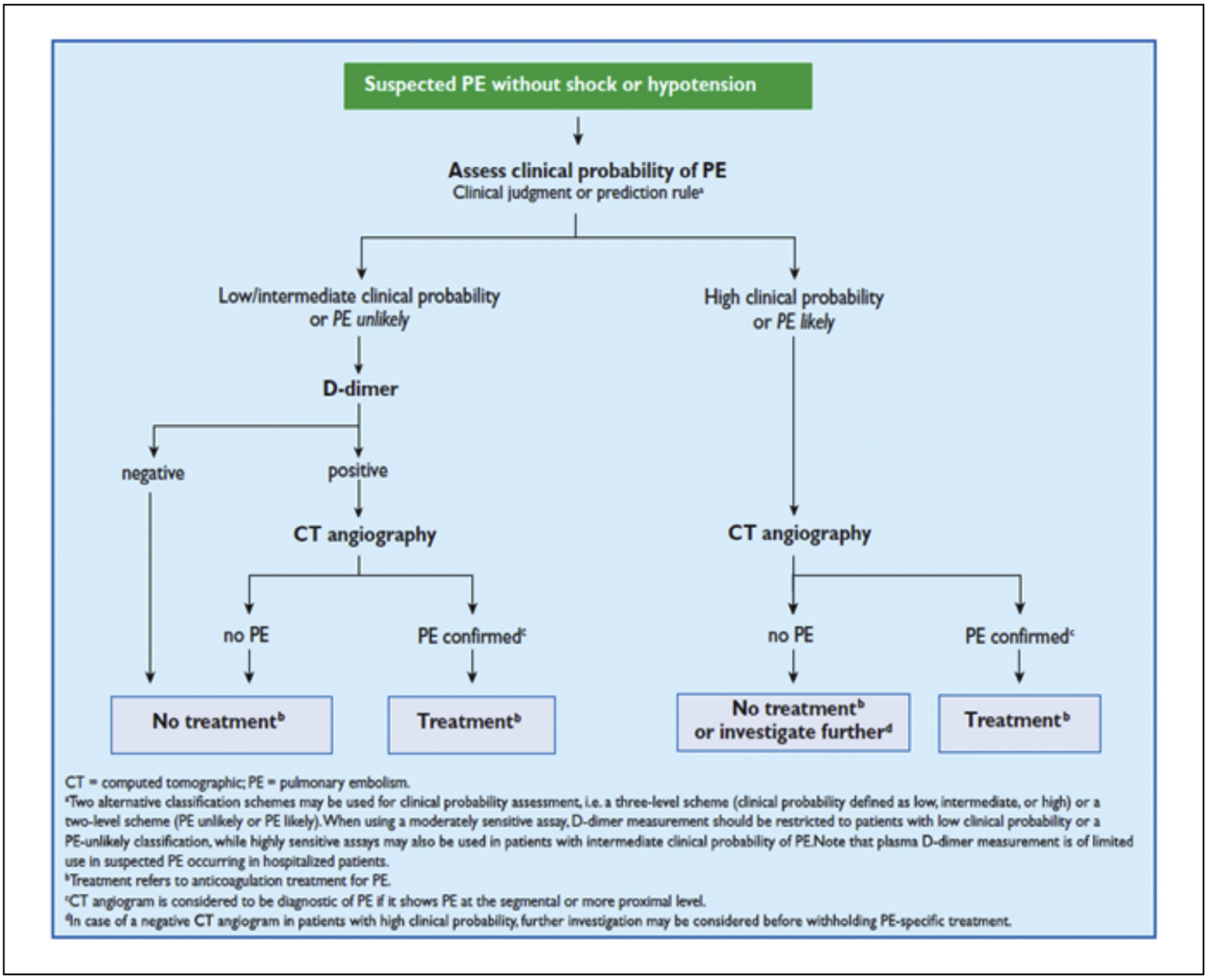

Fig. 4 – Proposed diagnostic algorithm for patients with suspected not high-risk pulmonary embolism.

to improve risk stratification of PE but their clinical relevance remains to be determined.

4.5 *Prognostic assessment strategy (recommendation I)*

For prediction of early (in-hospital or 30-day) outcome in patients with acute PE, both the PE-related risk and the patient's clinical status and comorbidities should be taken into consideration (Table 9). The risk-adjusted therapeutic strategies and algorithms recommended on the basis of this classification are discussed in the following section and summarized in Fig. 5. Further—*see* recommendations I.

Around one-third of PE patients are at low risk of an early adverse outcome (PESI Class I or II, or sPESI of 0). Normotensive

Recommendations I – (for prognostic assessment).

Recommendations	Class[a]	Level[b]
Initial risk stratification of suspected or confirmed PE—based on the presence of shock or persistent hypotension—is recommended to identify patients at high risk of early mortality.	I	B
In patients not at high risk, use of a validated clinical risk prediction score, preferably the PESI or sPESI, should be considered to distinguish between low- and intermediate-risk PE.	IIa	B
In patients at intermediate risk, assessment of the right ventricle with echocardiography or CT, and of myocardial injury using a laboratory biomarker, should be considered for further risk stratification.	IIa	B

CT = computed tomographic (pulmonary angiography); PE = pulmonary embolism; PESI = pulmonary embolism severity index; sPESI = simplified pulmonary embolism severity index.
[a] Class of recommendation.
[b] Level of evidence.

Table 7 – Original and simplified PESI.

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I: ≤65 points Very low 30-day mortality risk (0–1.6%)	*0 points* = 30-day mortality risk 1.0% (95% CI 0.0–2.1%)
	Class II: 66–85 points Low mortality risk (1.7–3.5%)	*≥1 point(s)* = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)
	Class III: 86–105 points Moderate mortality risk (3.2–7.1%)	
	Class IV: 106–125 points High mortality risk (4.0–11.4%)	
	Class V: >125 points Very high mortality risk (10.0–24.5%)	

b.p.m. = beats per minute; PESI = pulmonary embolism severity index.
[a] Based on the sum of points.

patients in PESI Class ≥III or sPESI of ≥1 are considered to constitute an intermediate-risk group and further risk assessment should be considered. Patients with both RV dysfunction and elevated troponin should be classified into an intermediate-high-risk category.

5 Treatment in the acute phase

5.1 *Haemodynamic and respiratory support*

Acute RV failure with resulting low cardiac index (CI) is the leading cause of death in patients with high-risk PE. Aggressive volume expansion is of no benefit, but modest (500 mL) fluid challenge may increase CI. Norepinephrine should probably be limited to hypotensive patients. The use of dobutamine and/or dopamine may be considered for patients with low CI, and normal blood pressure (BP). Epinephrine combines the beneficial properties of norepinephrine and dobutamine, without the systemic vasodilatory effects of the latter. According to data from small clinical studies, inhalation of nitric oxide may improve the haemodynamic status and gas exchange of patients with PE. Preliminary data suggest that levosimendan may restore right ventricular–pulmonary arterial coupling by combining pulmonary vasodilation with an increase in RV contractility.

Positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen RV failure;

Recommendations II – (for acute phase treatment).

Recommendations	Class[a]	Level[b]
PE with shock or hypotension (high-risk)		
It is recommended that intravenous anticoagulation with UFH should be initiated without delay in patients with high-risk PE.	**I**	**C**
Thrombolytic therapy is recommended.	**I**	**B**
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[c]	**I**	**C**
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[c]	**IIa**	**C**

PE = pulmonary embolism; UFH = unfractionated heparin.
[a] Class of recommendation.
[b] Level of evidence.
[c] If appropriate expertise and resources are available on site.

Recommendations III – (for acute phase treatment).

Recommendations	Class[a]	Level[b]
PE without shock or hypotension (intermediate-or low-risk)[c]		
Anticoagulation: combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B
Anticoagulation: new oral anticoagulants		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute phase parenteral anticoagulation.	I	B[d]
As an alternative to VKA treatment, administration of edoxaban[g] is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[e]	III	A
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of 'rescue' reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[f]	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[f]	IIb	B
Early discharge and home treatment		
Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.	IIa	B

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist.

[a] Class of recommendation.

[b] Level of evidence.

[c] See Table 9 for definition of the risk categories.

[d] RE-COVER and RE-COVER II are considered one large trial.

[e] Creatinine clearance <30 mL/min for rivaroxaban, dabigatran and edoxaban; and <25 mL/min for apixaban.

[f] If appropriate expertise and resources are available on site.

[g] *Caution*: Edoxaban is currently subject to regulatory review for the treatment of venous thromboembolism in the European Union.

therefore, positive end-expiratory pressure should be applied with caution. Low tidal volumes (approximately 6 mL/kg lean body weight) should be used in an attempt to keep the end-inspiratory plateau pressure <30 cm H_2O.

Experimental evidence, occasional case reports and patient series suggest that extracorporeal cardiopulmonary support can be an effective procedure in massive PE.

5.2 *Anticoagulation (recommendations II and III)*

The objective is to prevent both early death and recurrent symptomatic or fatal PE. The standard duration of anticoagulation is at least 3 months (also see Section 6). Acute-phase consists of administering parenteral anticoagulation [unfractionated heparin (UFH), low-molecular weight heparin (LMWH) or fondaparinux] over the first 5–10 days. Parenteral heparin should overlap with the initiation of a vitamin K antagonist (VKA); alternatively, it can be followed by administration of dabigatran or edoxaban. The treatment with rivaroxaban or apixaban should be started directly or after a 1–2 day administration of UFH, LMWH or fondaparinux.

5.2.1 *Parenteral anticoagulation*

In patients with high or intermediate clinical probability for PE (see Section 3), parenteral anticoagulation should be initiated whilst awaiting the results of diagnostic tests. Subcutaneous LMWH or fondaparinux are preferred, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia (HIT). On the other hand, UFH is recommended for patients in whom primary reperfusion is considered, as well as for those with creatinine clearance <30 mL/min, or severe obesity. LMWHs approved for the treatment of acute PE are listed in Table 10. LMWH and fondaparinux need no routine monitoring, but periodic measurement of anti-Xa levels may be considered during pregnancy.

Table 8 – Imaging and laboratory tests[a] for prediction of early[b] mortality in acute PE.

Test or biomarker	Cut-off value	Sensitivity, (95% CI)	Specificity, (95% CI)	NPV (95% CI)	PPV (95% CI)	OR or HR (95% CI)	No. of patients	Study design (reference)	Remarks
Echocardiography	Various criteria of RV dysfunction	74 (61–84)	54 (51–56)	98 (96–99)	8 (6–10)	2.4 (1.3–4.3)	1249	Metaanalysis	RV dysfunction on echocardiography or CT was one of the inclusion criteria in two randomized trials investigating thrombolysis in normotensive patients with PE.
CT angiography	RV/LV ≥ 1.0	46 (27–66)	59 (54–64)	93 (89–96)	8 (5–14)	1.5 (0.7–3.4)	383	Metaanalysis	
	RV/LV ≥ 0.9	84 (65–94)	35 (30–39)	97 (94–99)	7 (5–10)	2.8 (0.9–8.2)	457	Prospective cohort	
BNP	75–100 pg/m	85 (64–95)	56 (50–62)	98 (94–99)	14 (9–21)	6.5 (2.0–21)	261	Metaanalysis	The optimal cut-off value for PE has not been defined.
NT-proBNP	600 pg/mL	86 (69–95)	50 (46–54)	99 (97–100)	7 (5–19)	6.3 (2.2–18.3)	688	Prospective cohort[e]	NT-proBNP <500 pg/mL was one of the inclusion criteria in a single-armed management trial investigating home treatment of PE.
Troponin I	Different assays/ cut-off values[c]	NR	NR	NR	NR	4.0 (2.2–7.2)	1303	Metaanalysis	A positive cardiac troponin test was one of the inclusion criteria in a randomized trial investigating thrombolysis in normotensive patients with PE.
Troponin T	Different assays/ cut-off values[c]	NR	NR	NR	NR		682	Metaanalysis	
	14 pg/mL[d]	87 (71–95)	42 (38–47)	98 (95–99)	9 (6–12)	5.0 (1.7–14.4)	526	Prospective cohort[e]	
H-FABP	6 ng/mL	89 (52–99)	82 (74–89)	99 (94–99)	28 (13–47)	36.6 (4.3–304)	126	Prospective cohort[e]	

BNP = brain natriuretic peptide; CT = computed tomographic; H-FABP = heart-type fatty acid-binding protein; HR = hazard ratio; LV = left ventricular; NPV = negative predictive value; NR = not reported in the reference cited; NT-proBNP = N-terminal pro-brain natriuretic peptide; OR = odds ratio; PE = pulmonary embolism; PPV = positive predictive value; RV = right ventricular.

[a] The table shows the results of meta-analyses or, in the absence thereof, of the largest prospective cohort studies.

[b] In most studies, 'early' refers to the in-hospital period or the first 30 days after the index event.

[c] In the studies included in this meta-analysis, cut-off values for the cardiac troponin tests used corresponded to the 99th percentile of healthy subjects with a coefficient variation of <10%.

[d] High-sensitivity assay.

[e] These studies included only normotensive patients and used a combined outcome (all-cause death or major cardiovascular complications).

Table 9 – Classification of patients with acute PE based on early mortality risk.

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI >1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate-high	–	+	Both positive	
	Intermediate-low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative[e]	

PE = pulmonary embolism; PESI = Pulmonary embolism severity index; RV = right ventricular; sPESI = simplified Pulmonary embolism severity index.
[a] PESI Classes III–V indicate moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicate high 30-day mortality risk.
[b] Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV–LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0); hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On computed tomographic (CT) angiography (four-chamber views of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV (left ventricular) diameter ratio (with a threshold of 0.9 or 1.0).
[c] Markers of myocardial injury (e.g. elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).
[d] Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock.
[e] Patients in the PESI Classes I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate-low-risk category.
This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index.

5.2.2 *Vitamin K antagonists*

VKA should be initiated as soon as possible, preferably the same day as the parenteral anticoagulant. Anticoagulation with UFH, LMWH, or fondaparinux should be continued for at least 5 days and until the international normalized ratio (INR) has been 2.0–3.0 for two consecutive days. Warfarin can be started at a dose of 10 mg in younger (<60 years of age), otherwise healthy outpatients, and at a dose of 5 mg in older and hospitalized patients. Pharmacogenetic testing does not improve the quality of anticoagulation. Dosing based on the patient's clinical data is possibly superior to fixed loading regimens.

5.2.3 *New oral anticoagulants*

The results of the trials using NOACs in the treatment of VTE (Table 11) indicate that these agents are non-inferior (in terms of efficacy) and possibly safer (particularly in terms of major bleeding) than the standard heparin/VKA regimen. At the moment of publication of these guidelines, rivaroxaban, dabigatran and apixaban are approved for treatment of VTE in the European Union.

5.3 *Thrombolytic treatment*

Thrombolytic treatment of acute PE restores pulmonary perfusion more rapidly than anticoagulation. The approved regimens for PE are shown in Web Table 3. Most contraindications to thrombolysis (Web Table 4) should be considered relative in patients with life-threatening, high-risk PE.

UFH infusion should be stopped during administration of streptokinase or urokinase; it can be continued during rtPA infusion. It appears reasonable to continue anticoagulation with UFH for several hours after the end of thrombolytic treatment before switching to LMWH or fondaparinux. Thrombolysis can still be useful in patients who have had symptoms up to 14 days.

In the absence of haemodynamic compromise, the clinical benefits of thrombolysis have remained controversial for many years. Pulmonary Embolism Thrombolysis (PEITHO) trial was a multicentre, randomized, double-blind comparison of tenecteplase plus heparin vs. placebo plus heparin in acute PE patients with RV dysfunction and positive troponin. The primary efficacy outcome, a composite of all-cause death or haemodynamic decompensation/collapse within 7 days of randomization, was significantly reduced with tenecteplase (2.6% vs. 5.6% in the placebo group; $P < 0.015$; OR 0.44; 95% CI 0.23–0.88). The benefit of thrombolysis was mainly driven by a significant reduction in the rate of haemodynamic collapse (1.6% vs. 5.0%; $P < 0.002$).

Analysis of pooled data from trials using various thrombolytic agents and regimens reported intracranial bleeding rates between 1.9% and 2.2%.

5.4 *Surgical embolectomy*

Multidisciplinary teams have recently reintroduced the concept of surgical embolectomy for high-risk PE, and also for selected patients with intermediate-high-risk PE, particularly if thrombolysis is contraindicated or has failed. Surgical embolectomy has also been successfully performed in patients with right heart thrombi straddling the

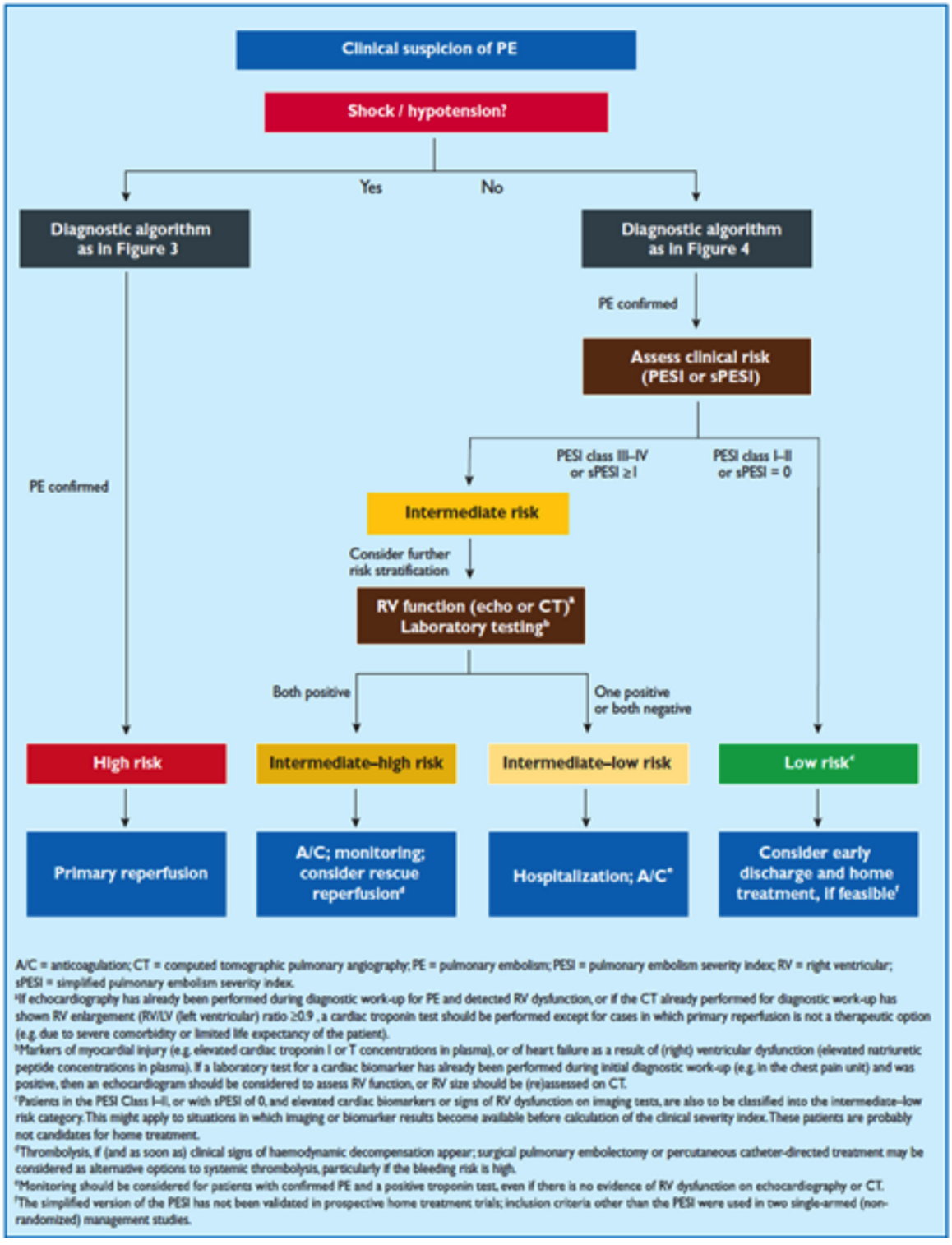

Fig. 5 – Risk-adjusted management strategies in acute PE (see Table 9 for definition of the risk categories).

interatrial septum through a patent foramen ovale. Preoperative thrombolysis increases the risk of bleeding, but it is not an absolute contraindication to surgical embolectomy.

5.5 *Percutaneous catheter-directed treatment*

For patients with absolute contraindications to thrombolysis, interventional treatment options include (i) thrombus

Table 10 – Low-molecular-weight heparins and pentasaccharide (fondaparinux) approved for the treatment of pulmonary embolism.

	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg[a]	Every 12 h Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b] or 200 IU/kg[b]	Every 12 h[b] Once daily[b]
Nadroparin[c]	86 IU/kg or 171 IU/kg	Every 12 h Once daily
Fondaparinux	5 mg (body weight <50 kg) 7.5 mg (body weight 50–100 kg) 10 mg (body weight >100 kg)	Once daily

All regimens administered subcutaneously.
IU = international units; LMWH = low-molecular-weight heparin.
[a] Once-daily injection of enoxaparin at the dosage of 1.5 mg/kg is approved for inpatient (hospital) treatment of PE in the United States and in some, but not all, European countries.
[b] In cancer patients, dalteparin is given at a dose of 200 IU/kg body weight (maximum, 18 000 IU) once daily over a period of 1month, followed by 150 IU/kg once daily for 5 months. After this period, anticoagulation with a vitamin K antagonist or an LMWH should be continued indefinitely or until the cancer is considered cured.
[c] Nadroparin is approved for treatment of PE in some, but not all, European countries.

Web Table 3 – Approved thrombolytic regimens for pulmonary embolism.

Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h Accelerated regimen: 1.5 million IU over 2 h
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12–24 h Accelerated regimen: 3 million IU over 2 h
rtPA	100 mg over 2 h; or 0.6 mg/kg over 15 min (maximum dose 50 mg)

IU = international units; rtPA = recombinant tissue plasminogen activator.

Web Table 4 – Contraindications to thrombolytic therapy.

Absolute contraindications[a]
- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications
- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

[a] Absolute contraindications to thrombolysis might become relative in a patient with immediately life-threatening high-risk PE.

fragmentation with pigtail or balloon catheter, (ii) rheolytic thrombectomy with hydrodynamic catheter devices, (iii) suction thrombectomy with aspiration catheters and (iv) rotational thrombectomy. On the other hand, for patients without absolute contraindications to thrombolysis, catheter-directed (eventually ultrasound accelerated) thrombolysis or pharmacomechanical thrombolysis are preferred approaches (see also Ref. [2]).

A review on interventional treatment included 35 non-randomized studies covering 594 patients.

5.6 *Venous filters (recommendations IV)*

There are no data to support the routine use of venous filters in patients with free-floating thrombi in the proximal veins. There is also no evidence to support the use of IVC filters in patients scheduled for systemic thrombolysis, surgical embolectomy, or pulmonary thromboendarterectomy.

5.7 *Early discharge and home treatment*

Crucial issue is to select patients with low risk of an adverse early outcome. Low-risk patients in the PESI Class I or II, and probably those with sPESI of 0 (Table 9), should be considered for early discharge and outpatient treatment. Table 12 summarizes recent multicentre trials that investigated the three-month clinical outcome of patients who were discharged early or treated entirely as outpatients. The first one was terminated prematurely because of an increased short-term mortality rate (2.8%, 2 patients) in the early-discharge arm. In the second larger trial, there was one non-VTE related death in each treatment group (0.6%). In a

Recommendations IV – (for venous filters).

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

IVC = inferior *vena cava*; PE = pulmonary embolism.
[a] Class of recommendation.
[b] Level of evidence.

Table 11 – Overview of phase III clinical trials with non-vitamin K-dependent new oral anticoagulants (NOACs) for the acute-phase treatment and standard duration of anticoagulation after VTE.

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEINDVT	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under w
	EINSTEIN-PE	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 mL/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

b.i.d. = bis in die (twice daily); CRNM = clinically relevant non-major; DVT = deep vein thrombosis; o.d. = omni die (once daily); PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism.

[a] Approved doses of dabigatran are 150 mg b.i.d. and 110 mg b.i.d.

Table 12 – Design of recent multicentre trials on home treatment of acute PE.

Author	Design	Inclusion criteria	Main exclusion criteria	Patients	Treatment
Aujesky	Open-label Randomized Non-inferiority 19 centres (ED) Discharge within 24 h vs. inpatient therapy	Age ≥18 years Confirmed acute PE PESI Class I or II	BP <100 mm Hg Pain needing opioids Active bleeding or high risk Extreme obesity CrCl <30 mL/min HIT history Barriers to home treatment	344 (of 1557 screened)	*Both arms:* enoxaparin s.c. twice daily; overlap with VKA (starting 'early')
Otero	Open-label Randomized 9 centres Discharge after 3–5 days vs. inpatient therapy	Age ≥18 years Confirmed acute PE Low-risk by Uresandi clinical prediction rule[350]	Haemodynamic instability Troponin T ≥0.1 ng/mL RV dysfunction (TTE) High bleeding risk Severe comorbidity O2 saturation <93% COPD, asthma Extreme obesity	132 (of 1016 screened)	*Both arms:* LMWH s.c. overlap with VKA (starting day 10)
Zondag	Prospective cohort 12 centres (ED) All treated as outpatients, discharge within 24 hours	Age ≥18 years Confirmed acute PE	Haemodynamic instability Active bleeding or high risk Oxygen requirement CrCl <30 mL/min Hepatic failure HIT history Barriers to home treatment	297 (of 581 screened)	Nadroparin s.c. once daily; overlap with VKA (starting day 1)
Agterof	Prospective cohort 5 centres (ED) Discharge within 24 h	Age ≥18 years Confirmed acute PE NT-proBNP <500 pg/mL	Haemodynamic instability Active bleeding or high risk Severe comorbidity Pain with i.v. analgesia Oxygen requirement Creatinine >150 μmol/L Barriers to home treatment	152 (of 351 screened)	LMWH s.c. once daily; overlap with VKA (starting 'early')

BP = (systolic) blood pressure; COPD = (severe) chronic obstructive pulmonary disease; CrCl = creatinine clearance; ED = emergency department (s); HIT = heparin-induced thrombocytopenia; i.v. = intravenous; LMWH = low-molecular-weight heparin; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary embolism severity index (see Table 7); RV = right ventricular; s.c. = subcutaneous; TTE = transthoracic echocardiography; VKA = vitamin K antagonist.

meta-analysis of 14 (mostly cohort-) studies, the pooled incidences of recurrent VTE, major bleeding and total mortality did not differ significantly between outpatients, patients discharged early, and those treated as inpatients.

5.8 *Therapeutic strategies*

An algorithm and principles of the recommended therapeutic strategies for acute PE are shown in Fig. 5 and recommendations II+III.

5.9 *Areas of uncertainty*

Further trials and investigation are necessary for risk stratification in not-high-risk patients with PE, for postulation of therapeutic strategy in intermediate-high-risk PE, and for creation of the criteria for early discharge and home treatment of low-risk patients with PE.

6 Duration of anticoagulation (recommendation V)

The aim of anticoagulant treatment in patients with PE is to prevent VTE. Clinical trials evaluating duration of anticoagulant treatment showed, that patients with PE should receive at least 3 months of anticoagulant treatment. The risk of recurrent VTE after withdrawal of anticoagulant treatment after 3, 6 or 12 months is similar. Indefinite treatment reduces the risk of recurrence of VTE by about 90%, but this reduction is accompanied by a 1% or higher annual risk of major bleeding.

Active cancer is a major risk factor for recurrence of VTE. At least 3–6 months of treatment with LMWH is recommended for patients with VTE and cancer and after first 6 months treatment with LMWH or VKA is recommended as long as the disease is considered active.

The risk for recurrent VTE after discontinuation of anticoagulant treatment in patients with provoked PE is approximately 2.5% per year.

The risk for recurrent VTE after discontinuation of anticoagulant treatment in patients with unprovoked PE is approximately 4.5% per year. Indefinite anticoagulation therapy should be considered for patients with a first unprovoked proximal DVT or PE and for patients with lupus anticoagulant, deficit of protein C and S, with homozygous factor V Leiden and homozygous prothrombin G20210A. The option to withdraw anticoagulant treatment should periodically be re-assessed. Lifelong treatment is recommended for most patients with second unprovoked DVT or PE. Therapy with

Recommendations V – (for duration of anticoagulation after pulmonary embolism).

Recommendations	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant veracious treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[c]	IIa	B[d]
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C
In patients who refuse to take or unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B
For patients with PE and cancer, weight adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist.
[a] Class of recommendation.
[b] Level of evidence.
[c] Long-term data on patients taking new oral anticoagulants for secondary PE prophylaxis are not yet available.
[d] B refers to the evidence available for each drug separately.

aspirin after termination of oral anticoagulation could particularly reduce the risk of recurrence (recommendations V).

6.1 *New oral anticoagulants for extended treatment*

Three NOACs (dabigatran, rivaroxaban, and apixaban) have been evaluated in the extended treatment in patients with VTE. The results are in line with the studies that tested NOACs in the acute phase treatment and standard duration of anticoagulation after PE or VTE. They indicate that NOACs are both effective (in terms of prevention of symptomatic or fatal recurrence of VTE) and probably safer than standard VKA regimens (recommendations V and Table 13).

7 Chronic thromboembolic pulmonary hypertension

7.1 *Epidemiology*

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct subgroup of PH caused by chronic obstruction of pulmonary arteries. CTEPH may occur in approximately five individuals per million population per year.

7.2 *Pathophysiology*

CTEPH is primarily caused by pulmonary thromboembolism. Clinical history of VTE is reported in 80% of patients with CTEPH. CTEPH does not share the same risk factor profile with VTE and has been associated with only a few specific thrombophilic factors (presence of lupus anticoagulant, antiphospholipid antibodies and elevated level of factor VIII). In addition, splenectomy, ventriculoatrial shunt for hydrocephalus therapy, inflammatory bowel disease, and chronic osteomyelitis are associated with a higher incidence of CTEPH. Apart from major pulmonary vascular obstruction, the pathophysiology of CTEPH includes a pulmonary microvascular disease.

7.3 *Clinical presentation and diagnosis*

The median age of patients at diagnosis of CTEPH is 63 years, both genders are equally affected. Clinical symptoms and signs are non-specific or absent in early CTEPH. The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation (mean pulmonary arterial pressure ≥25 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg, at least one perfusion defect detected by V/Q scintigraphy, or detected pulmonary artery obstruction). V/Q lung scintigraphy remains the main first-line imaging modality for CTEPH. MDCTA alone cannot rule out the disease. The final step in the diagnostic pathway is right heart catheterization and selective pulmonary angiography (Fig. 6).

7.4 *Treatment and prognosis (recommendation VI)*

Pulmonary endarterectomy (PEA) under deep hypothermia and circulatory arrest is the treatment of choice. The majority of patients experience substantial relief from symptoms and near-normalization of haemodynamics after the surgery. General criteria of operability include pre-operative New York Heart Association functional class II–IV and the surgical accessibility of thrombi.

Balloon pulmonary angioplasty could be an alternative for selected patients with non-operable CTEPH.

Routine cava filter placement is not justified by the available evidence.

Optimal medical treatment for CTEPH consists of lifelong anticoagulants (no data exist on the efficacy and safety of NOACs), diuretics, and oxygen.

Table 13 – Clinical trials on extended treatment of venous thromboembolism.

Study	Active[a]	Design	Comparator	Expected reduction	Treatment duration	No. patients enrolled	VTE in control group	Risk reduction for recurrent VTE	Major or CRNM bleeding in active[a] group
RE-SONATE	Dabigatran 150 mg b.i.d.[c]	Placebo	Superiority	70%	6 months	1343	5.6%	92%	5.3%
RE-MEDY	Dabigatran 150 mg b.i.d.[c]	Warfarin (INR 2–3)	Noninferiority	Absolute increase, <2.8	18–36 months	2856	1.3%	Risk difference, 0.38% vs. VKA	5.6% (vs. 10.2% in warfarin arm)
EINSTEIN Ext	Rivaroxaban 20 mg daily	Placebo	Superiority	70%	6–12 months	1196	7.1%	82%	6.0%
AMPLIFY Ext	Apixaban 5.0 mg b.i.d.	Placebo	Superiority	41%	12 months	2486	8.8%	80%	4.2%
	Apixaban 2.5 mg b.i.d.[d]							81%	3.0%
WARFASA	Aspirin	Placebo	Superiority	40%	≥24 months	402	11.2%[b]	40%	1.0%[b]
ASPIRE	Aspirin	Placebo	Superiority	30%	4 years (actual, 27 months)	822	6.5%[b]	26%	1.7%[b]

b.i.d. = bis in die (twice daily); CRNM = clinically relevant non-major; SD = standard deviation; VKA = vitamin K antagonists; VTE = venous thromboembolism.

[a] 'Active' denotes in the Table the direct oral thrombin or factor Xa inhibitor (or aspirin) tested; the comparator arm also received anticoagulation (a vitamin K antagonist) in some of the studies.

[b] Incidence per patient-year.

[c] Approved doses of dabigatran are 150 mg b.i.d. and 110 mg b.i.d.

[d] This is the approved dose of apixaban for extended treatment.

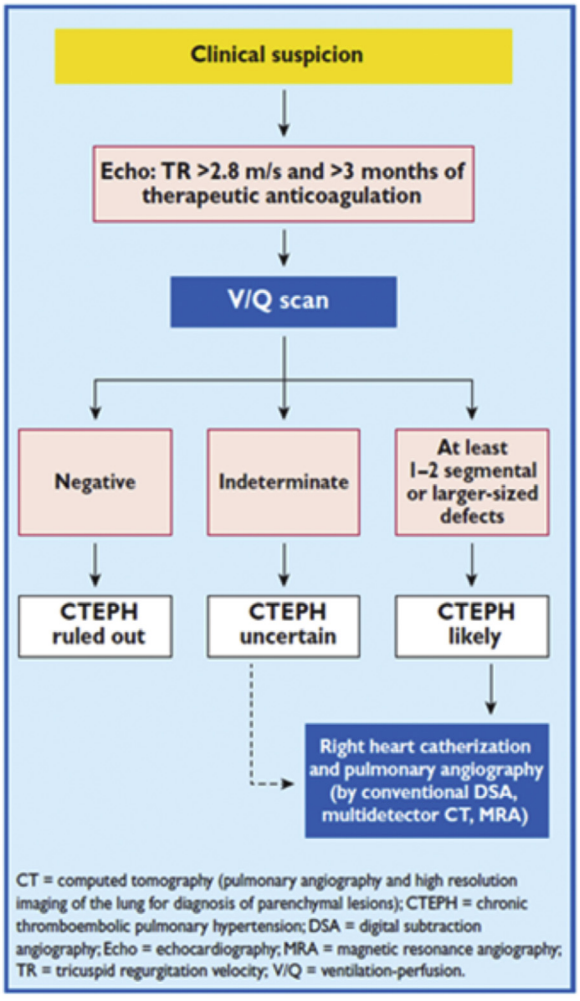

Fig. 6 – Algorithm for the diagnosis of chronic thromboembolic pulmonary hypertension. Adapted from Lang et al. (2010).

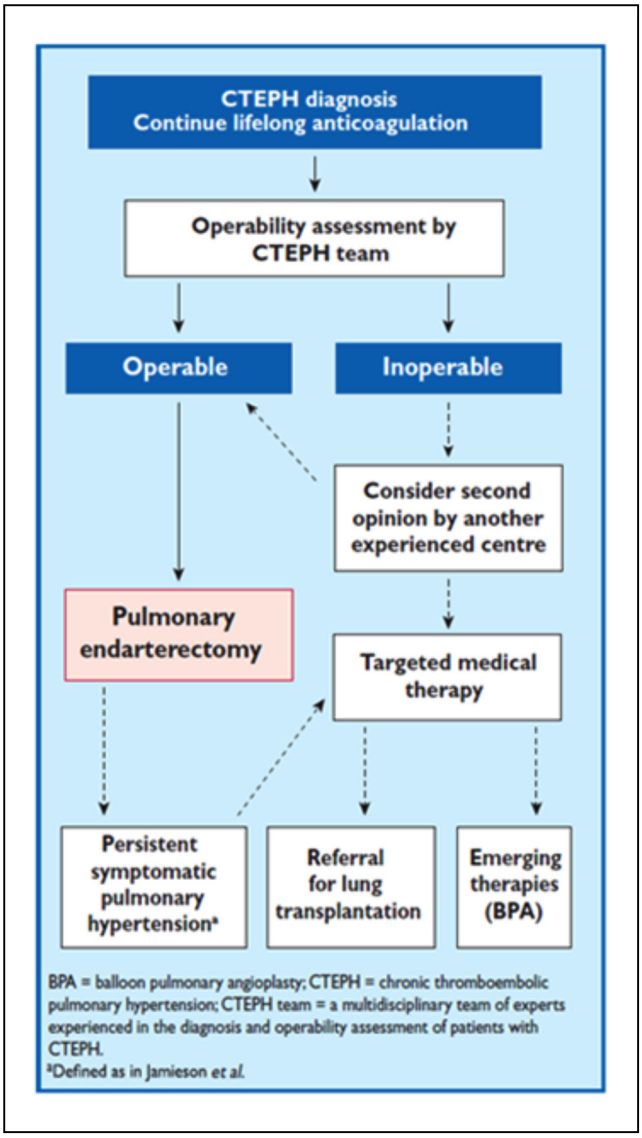

Fig. 7 – Algorithm for the treatment of chronic thromboembolic pulmonary hypertension. Adapted from Ghofrani et al. (2013).

Pulmonary microvascular disease in CTEPH has provided the rationale for use of drugs approved for pulmonary arterial hypertension in inoperable patients and in patients with persistent or residual pulmonary hypertension after PEA. Only riociguat (oral stimulator of soluble guanylate cyclase) received approval for use in this indication (Fig. 7 and recommendations VI).

8 Specific problems

8.1 *Pregnancy (recommendation VII)*

PE is the leading cause of pregnancy-related maternal death in developed countries.

The risk of PE is higher in the post-partum period, particularly after a caesarean section.

8.1.1 *Diagnosis*

Exposure of the foetus to ionizing radiation is a concern when investigating suspected PE (Table 14).

The usual D-dimer cut-off value should apply to rule out PE in pregnancy. If the D-dimer result is abnormal, diagnostic work-up may continue with lower-limb CUS (since proximal DVT warrants anticoagulation and makes thoracic imaging unnecessary). If ultrasonography is negative, the diagnosis should be pursued. A perfusion scan and MDCTA are equally safe for ruling out PE in pregnancy. Lung scintigraphy may be preferred over MDCTA because it avoids the high radiation dose delivered to the female breast (Table 14).

8.1.2 *Treatment*

The treatment of PE in pregnancy is based on heparin anticoagulation. Treatment should consist of a weight-adjusted dose of LMWH. Adaptation according to anti-Xa

Recommendations VI – (for chronic thromboembolic pulmonary hypertension).

Recommendations	Class[a]	Level[b]
In PE survivors with persistent dyspnoea, diagnostic evaluation for CTEPH should be considered.	IIa	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C
It is recommended that, in all patients with CTEPH, the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C
Surgical PEA is recommended for patients with CTEPH.	I	C
Riociguat is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon, or have persistent/recurrent CTEPH after surgical treatment.	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B

CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PEA = pulmonary endarterectomy.
[a] Class of recommendation.
[b] Level of evidence.

Table 14 – Estimated radiation absorbed in procedures used for diagnosing PE.

Test	Estimated foetal radiation exposure (mSv)	Estimated maternal radiation exposure to breast tissue (mSv)
Chest X-ray	<0.01	0.01
Perfusion lung scan with technetium-99 m labelled albumin		
Low dose: 40 MBq	0.11–0.20	0.28–0.50
High dose: 200 MBq	0.20–0.60	1.20
Ventilation lung scan	0.10–0.30	<0.01
Computed tomographic angiography	0.24–0.66	10–70

Adapted from Bajc et al. (2009) and Chunilal et al. (2009).
mSv = milisievert; PE = pulmonary embolism.

monitoring may be considered in women at extremes of body weight or with renal disease.

Unfractionated heparin is not contraindicated in pregnancy. Fondaparinux should not be used in pregnancy due to the lack of data. VKAs and NOACs are contraindicated in pregnant patients.

After delivery, heparin treatment may be replaced by VKAs and it should be administered for at least 6 weeks after delivery and with a minimum overall treatment duration of 3 months. VKAs can be given to breast-feeding mothers.

The risk of complications of thrombolytic treatment for the mother may be similar to that in the non-pregnant population. It should not be used peripartum, except for critical cases (recommendations VII).

8.2 *Pulmonary embolism and cancer (recommendation VIII)*

The overall risk of venous thromboembolism in cancer patients is four times as great as in the general population. Patients receiving chemotherapy have a six-fold increase in the adjusted risk ratio for VTE compared with a healthy population, prophylactic anticoagulation is not routinely recommended. The risk of VTE increases over 90-fold in the first 6 weeks after cancer surgery. Continued vigilance is therefore necessary, as currently recommended prophylactic anticoagulation covers only 30 days after cancer surgery (recommendations VIII).

Recommendations VII – (for pulmonary embolism in pregnancy).

Recommendations	Class[a]	Level[b]
Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.	I	C
D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.	IIb	C
Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.	IIb	C
Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray.	IIb	C
CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available.	IIa	C
A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.	I	B

CT = computed tomographic; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism.
[a] Class of recommendation.
[b] Level of evidence.

Recommendations VIII – (for pulmonary embolism in cancer).		
Recommendations	Class[a]	Level[b]
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

LMWH = low molecular weight heparin; PE = pulmonary embolism.
[a] Class of recommendation.
[b] Level of evidence.

8.3 *Non-thrombotic pulmonary embolism*

Non-thrombotic PE can be caused by different cell types or by bacteria, fungi, parasites, foreign materials, and gas. Symptoms are similar to those of acute VTE. Diagnosis of non-thrombotic PE can be a challenge (microemboli cannot be detected on CT and images and clinical evidence is limited).

8.3.1 *Septic embolism*

Septic embolism is commonly associated with right-sided endocarditis. *Staphylococcus aureus* is the most common pathogen, the incidence of anaerobic gram positive and -negative bacteria, bacteroides species, and fungi is increasing.

8.3.2 *Foreign-material pulmonary embolism*

The incidence of foreign-material PE is increasing due to use of interventional techniques in modern medicine. The material may cause further thrombosis and sepsis.

8.3.3 *Fat embolism*

Pulmonary involvement in fat embolism is not only due to vascular obstruction but also to the release of substances triggering an inflammatory cascade. In most cases the condition is self-limiting. Treatment is supportive.

8.3.4 *Air embolism*

Venous air embolization is often an iatrogenic complication of the manipulation of venous catheters. The lethal volume of air after injection in humans is estimated to range from 100 to 500 mL. CT scanning is the most sensitive diagnostic test. Treatment includes maintenance of the circulation, prevention of further entry of gas, volume expansion, left lateral decubitus position and administration of oxygen.

8.3.5 *Amniotic fluid embolism*

Estimated incidences range between 1.9 and 2.5 cases per 100 000 maternities. Mortality is high (up to 21%). Management is supportive.

8.3.6 *Tumour embolism*

Pulmonary intravascular tumour emboli are seen in up to 26% of autopsies of patients with solid malignancies. Tumour microembolism may mimic many lung conditions, macroembolism is indistinguishable from VTE. Treatment should target the underlying malignant disease.

REFERENCES [1]

[1] 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism, Authors/Task Force Members: Stavros Konstantinides, Adam Torbicki, Giancarlo Agnelli, Nicolas Danchin, David Fitzmaurice, Nazzareno Galiè, J. Simon R. Gibbs, Menno Huisman, Marc Humbert, Nils Kucher, Irene Lang, Mareike Lankeit, John Lekakis, Christoph Maack, Eckhard Mayer, Nicolas Meneveau, Arnaud Perrier, Piotr Pruszczyk, Lars H. Rasmussen, Thomas H. Schindler, Pavel Svitil, Anton Vonk Noordegraaf, Jose Luis Zamorano, Maurizio Zompatori. European Heart Journal 35 (2014) 3033–3069.

[2] 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism—*web addenda*, Authors/Task Force Members: Stavros Konstantinides, Adam Torbicki, Giancarlo Agnelli, Nicolas Danchin, David Fitzmaurice, Nazzareno Galiè, J. Simon R. Gibbs, Menno Huisman, Marc Humbert, Nils Kucher, Irene Lang, Mareike Lankeit, John Lekakis, Christoph Maack, Eckhard Mayer, Nicolas Meneveau, Arnaud Perrier, Piotr Pruszczyk, Lars H. Rasmussen, Thomas H. Schindler, Pavel Svitil, Anton Vonk Noordegraaf, Jose Luis Zamorano, Maurizio Zompatori. European Heart Journal 35 (2014) http://dx.doi.org/10.1093/eurheartj/ehu283.

[1] For all other references see original full text ESC document [1].